APPENDIX B

TF-210

Disposal of used fentanyl patches

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Fentanyl is a potent opioid that has been abused both on the street and by health care professionals.[1-3] The transdermal delivery system for fentanyl (the fentanyl patch) can be abused even after it has been discarded. We describe here a case of transdermal fentanyl abuse and discuss how existing laws and practices fail to make used patches inaccessible. We also offer recommendations for the proper disposal of transdermal fentanyl.

Case report

A 31-year-old man collapsed face down on the bank of a pond while fishing. He had complained of weakness and nausea before collapsing, and his companion's attempts to rouse him were unsuccessful. Emergency personnel arrived 10 minutes later and found the man to be diaphoretic, cyanotic, and breathing shallowly twice a minute. The blood pressure was 210/110 mg Hg, and the heart rate was extremely high (rate unrecorded). Bowel sounds and the gag reflex were absent. The patient was intubated and brought to the hospital emergency department in cardiac arrest. Resuscitative efforts, which included the administration of sodium bicarbonate, epinephrine, lidocaine, and intravenous fluids, were unsuccessful, and the patient was pronounced dead 103 minutes after his collapse.

The patient had been taking propoxyphene with acetaminophen for migraine headaches. A few weeks before his death he had undergone a root canal procedure and received unspecified analgesics (but not fentanyl). He had worked as a transporter for a funeral home.

Postmortem toxicological studies were negative for the presence of ethanol, cocaine, morphine, volatile agents, and organic bases; trace amounts of propoxyphene and its metabolite norpropoxyphene were detected. The serum fentanyl concentration was 15 μg/L. (Normal therapeutic concentrations of fentanyl range from 1 to 3 μg/L, and central nervous system depression occurs in this range.[2] The fentanyl concentration in suicidal and accidental overdoses is often less than 5 μg/L.) The serum lidocaine concentration was 2 mg/L, consistent with the administration of the drug during the attempted resuscitation. Death was attributed to fentanyl poisoning.

The medical examiner's investigation revealed that the most likely source of the decedent's fentanyl was two used transdermal fentanyl patches (one 75-μg/hr and one 100-μg/hr patch [Duragesic, Janssen]). The decedent had on the day of his death transported the body of a recently deceased woman from a local nursing home. The patches had been applied the previous day but not been removed before the body was transported. The nursing home had no policy concerning removal of patches from deceased patients. If the patches had been worn by the woman for 24 hours, then the patches would theoretically have had about 13.3 mg of fentanyl remaining in them.

Disposal of fentanyl patches

Published reports make it clear that transdermal fentanyl can be abused,[4,5] yet the laws regarding its disposal are vague. Federal law does not describe the actual manner in which controlled substances in general should be destroyed, and there are no specific regulations on how used fentanyl patches should be destroyed or made unavailable to unauthorized persons (Black JR, Drug Enforcement Administration, personal communication, 1996 Apr 18). Individual states are generally no more specific in describing the proper destruction of controlled substances.

We reviewed the procedures for the disposal of used fentanyl patches at two academic teaching hospitals in North Carolina. In some instances used patches were cut before being discarded in the trash, and in others they were flushed down the toilet. Most commonly,

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the patches were simply discarded unaltered (not necessarily into the biohazard waste receptacle).

The lack of adequate federal and state regulatory controls and the resultant laxity in disposal make used fentanyl patches relatively easy to obtain at health care facilities. Institutional initiatives for the appropriate disposal of the patches, if they necessitate substantial documentation, may not be readily accepted by health care professionals already overburdened with paperwork. Nevertheless, adequate disposal of used patches might prevent some illicit use and reduce the expenditures associated with fentanyl abuse.

Recommendations

Education would be a reasonable first step in addressing the problem of fentanyl patch abuse. Health care providers could be taught about the potentially lethal amounts of fentanyl remaining in used patches and about the patches' unique pharmacokinetic properties.

The key to proper patch disposal is the institution of procedures that make discarded patches unusable and that comply with applicable laws (as those laws concern, for example, the persons authorized to destroy controlled substances and the need for witnesses and cosignatures). The most foolproof method would be to collect from all patients all used narcotics, which would then be incinerated. In institutions without an incinerator, used patches collected from inpatients could either be cut and flushed down the toilet or placed in separately marked biohazard waste receptacles. Cutting the patch before flushing would allow the gel to diffuse in sewage water such that the amount of drug left in a found patch fragment would be reduced. If patches are cut, gloves should be worn to prevent the gel from touching the skin of the health care worker and being absorbed, and the scissors should be cleaned with alcohol afterward. Another possibility would be an exchange program in which used or unused patches were turned in before new patches or other controlled substances were dispensed.[5,6]

Outpatients should be strongly encouraged to follow the manufacturer's directions for patch disposal. The manufacturer states that unneeded patches should be flushed down the toilet—used ones after being folded so that the adhesive side sticks to itself, and unused ones after being removed from the pouch.[7] Cutting patches into several pieces before flushing may be reasonable for outpatients who want to ensure that no one in the immediate vicinity has access to a discarded patch. Again, gloves should be worn, and the scissors should be cleaned after the cutting.

Conclusion

Fentanyl patches, if not disposed of properly, can be abused and cause harm or death. Federal and state laws and most institutional procedures do not ensure that used patches are rendered unusable. Health care professionals should institute practices that make the abuse of discarded fentanyl patches impossible.

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CASE REPORT

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Fatal Fentanyl Intoxication Following Excessive Transdermal Application*

REFERENCE: Edinboro LE, Poklis A, Trautman D, Lowry S, Backer R, Harvey CM. Fatal fentanyl intoxication following excessive transdermal application. J Forensic Sci 1997;42(4):741–743.

ABSTRACT: The case history and toxicological findings of a fatal fentanyl intoxication due to the application of multiple transdermal patches are presented. An 83 year-old white female with terminal cancer was found dead with three 100 mg/h fentanyl patches on her chest. The autopsy and subsequent histological studies revealed extensive areas of gastric carcinoma, a large atrial tumor, ulceration of esophagus, metastasis of peripancreatic lymph nodes and a recent surgical removal of part of the lower lobe of the left lung. Toxicological analysis by GC/MS yielded fentanyl concentrations of blood, 25 ng/mL; brain, 54 ng/g; heart 94 ng/g; kidney 69 ng/g; and liver 104 ng/g. The cause of death was determined to be fentanyl overdose and the manner of death was ruled undetermined as the investigation was unable to conclusively establish whether this was an accidental overdose, a suicide, an assisted suicide, or possibly a homicide. This case demonstrates the need for caution in self-administration of transdermal fentanyl patches, in particular, the dangers inherent in the application of multiple patches which can result in the release of potentially toxic or lethal doses.

KEYWORDS: forensic science, forensic toxicology, death, fentanyl, transdermal administration, drug overdose, poisoning

Fentanyl is a synthetic narcotic analgesic of high potency (80 times morphine) and short duration of action (1). Due to lessened side effects, including shorter duration of respiratory depression, fentanyl is the analgesic of choice in surgical procedures performed in the U.S.A. Plasma concentrations of fentanyl of 2 to 5 ng/mL are sufficient to induce surgical analgesia and respiratory depression (2). In addition to use as a surgical analgesic, fentanyl is also prescribed for the management of chronic pain for patients requiring opiate analgesia. Recently, fentanyl has become available in 2.5, 5, 7.5, and 10 mg transdermal patches which release 25, 50, 75, and 100 μg/hr, respectively, for over 72 h (3). Measurable serum concentrations of fentanyl occur within 2 h of application of the patches (4). Blood, serum, and plasma concentrations are similar to those obtained following equivalent I.V. doses (3,5). Fentanyl has a large apparent volume of distribution (60–300 L) and is primarily metabolized in the liver by dealkylation (2). The elimination of fentanyl is highly dependent on the age and physiological status of the patient.

Fentanyl's therapeutic popularity has not been without problems. As a potent narcotic, fentanyl has become an abuse problem among health professionals, including anesthesiologists, physicians, pharmacists, and nurses (6,7). Recreational abuse of fentanyl is extremely dangerous due to the low concentrations necessary to induce respiratory depression. Several overdose deaths of health professionals have been reported (8–11).

More recently, however, recreational abuse of fentanyl by non-health professionals has been reported involving ingestion, injection, or smoking of fentanyl transdermal patches (12–14). As the use of transdermal patches increases for the management of chronic pain, it appears that other forms of therapeutic mis-adventures may be occurring. For example, patients may apply more than one patch at a time in order to experience enhanced pain relief. As the patches are capable of delivery therapeutic doses of fentanyl, placement of multiple patches would result in fentanyl toxicity including death.

The following case is presented as an example of fentanyl toxicity, as a direct result or compounding factor, in the death of an elderly woman found with multiple fentanyl transdermal patches on her body.

Case Report

Autopsy Findings

An 83-year-old white female was found dead with three 100 ug/h fentanyl patches on her chest. The woman had been diagnosed with terminal cancer and was using fentanyl patches for treatment of pain. The autopsy and subsequent histological studies revealed extensive areas of gastric carcinoma, a large antral tumor, ulceration of esophagus, metastasis of peripancreatic lymph nodes and a recent surgical removal of part of the lower lobe of the left lung. A careful examination of the body revealed no apparent injection sites.

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Toxicological Analysis

Initial Analysis—Blood was initially screened for ethanol using an enzymatic/radiant energy technique; salicylates by trinders reagent and morphine by radioimmunoassay (RIA). Urine as analyzed for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and phencyclidine by enzyme immunoassay (Emit II, Bahring Diagnostics, San Jose, CA). Additionally, both blood and urine were screened for fentanyl by RIA (Diagnostic Products, Los Angles, CA) (15).

Quantitative Fentanyl Analysis

GC/MS quantitation of fentanyl was based on previously published methods (16–18). To separate 5.0 g samples of heart, liver, kidney, and brain tissue were added 5.0 mL of distilled water. The samples were then homogenized in a mini-adapted Waring Blender. To 5.0 mL aliquots of tissue homogenates and 2.0 mL aliquots of calibrators, drug free blood, and autopsy blood samples was added 50 ng/mL of fentanyl-d5 (Radian Corp. Austin, TX) as the internal standard. To each aliquot 2.0 mL of pH 9 saturated borate buffer was added, followed by 8.0 mL of n-chlorobutane. The aliquots were vortexed for 15 min, then centrifuged for 5 min and the organic top layer was drawn off into a new tube. Then 2.0 mL 0.1M HCl was added to each extract which was the vortexed for 15 min and centrifuged for 5 min. The bottom aqueous layers were then removed using a 2 mL glass pipette and placed into clean 15 mL centrifuge tubes. The pH of the solutions were then adjusted to greater than pH 9 with the addition of 1.0 mL of 2 N NaOH. The solution was extracted with 3.0 mL of n-chlorobutane by vortexing for 10 min followed by centrifuging for 5 min and organic layers were then transferred to clean 12 by 75 mm test tubes and evaporated to dryness in a Savant Evaporator/Concentrator for 20 min (initial 10 min with radiant cover on). The residues were reconstituted with 500 μL n-chlorobutane, vortexed, and evaporated to dryness at 80°C under dry nitrogen. The resultant residues were reconstituted with 50 μL of n-chlorobutane of which 2.5 μL aliquots were injected into the GC/MS.

GC/MS analysis was performed on a Hewlett-Packard (Avondale, CA) 5890 GC equipped with a 12.5 m by 0.2 mm (ID) by 0.33 μm (film thickness) cross linked 5% phenyl silicone capillary column with a 12 m guard column (Restek, Bellefonte, PA) connected to a Hewlett-Packard 5971-A mass selective detector. Data processing was performed with a HP Chemstation (Version 3.2 software) in the scan mode monitoring m/z ions from 44–600. The GC/MS was operated in the splitless mode with a helium carrier gas linear velocity of 20 mL/min. Initial oven temperature was 200°C for 1 min with an injection port temperature of 250°C. The temperature was ramped at 15°C/min to a final temperature of 280°C which was held for 2.5 min. Data were collected in the SIM mode monitoring m/z ions 245, 146, 189 (fentanyl) and 250, 151, 194 (fentanyl-d5) with a dwell time of 50 ms for each ion.

Calibration

Fentanyl working standard (1μg/mL) was prepared by diluting 1:100 with methanol a 100 μg/mL fentanyl stock standard (Radian Corp.). A calibration curve (0.5, 2.0, 10.0, and 50.0 ng/mL fentanyl) was prepared by adding the appropriate volume of fentanyl working standard to 2.0 mL of drug free whole blood. The calibrators were vortexed and allowed to equilibrate 1 h prior to use.

Results

Initial toxicological analysis of blood and urine failed to disclose the presence of commonly encountered drugs of abuse and alcohol. RIA fentanyl analysis yielded 14 ng/mL in urine and 10 ng/mL in blood (extrapolated from the urine calibration curve). The results of GC/MS fentanyl analysis of the decedents' blood and tissues are presented in Table 1. Fentanyl blood and tissue concentrations greatly exceed those associated with therapeutic administration (4–6) and are consistent with or greatly exceed those previously reported in cases of fatal intoxication (8–11,14,19,20). Fentanyl blood concentrations in these cases ranged from 0.1–28 ng/mL with liver and kidney valves ranging up to 76 and 42 ng/mL, respectively.

The cause of death was determined to be fentanyl overdose and the manner of death was ruled undetermined. The investigation was unable to conclusively establish whether this was an accidental overdose, a suicide, an assisted suicide, or possibly a homicide.

Discussion

The use of fentanyl transdermal release patches provides the advantages of maintaining a constant therapeutic serum concentration similar to constant I.V. infusion while circumventing erratic gastrointestinal absorption and first pass metabolism of oral preparations (3,4). Thus, these dosage forms have proven efficacious for the long term management of cancer related pain. No doubt the out-patient prescribing of transdermal patches will increase in the future. To prevent fentanyl toxicity, both patient and care giver must be properly instructed on the use and hazards of fentanyl patches.

In this case, the decedent was instructed to apply one 100 ug/h patch once every 2–3 days as indicated for cancer related pain. Application of a single 100 μg/h transdermal fentanyl patch would be expected to result in a maximal plasma fentanyl concentrations of 2 to 3.8 ng/mL at 25–72 h after application (4). It appears that the application of multiple transdermal fentanyl patches resulted in an overdose for this woman. Theoretically, three 100 μg/h patches would be expected to produce a blood fentanyl concentration of approximately 10 ng/mL within 24 h of application. The blood concentration of fentanyl in this case was 25 ng/mL indicating that this woman may have been using multiple patches for several days. Additionally, due to her age, the metabolism of fentanyl may have been markedly decreased. Therefore it is possible that the time frame for development of toxicity would have been shortened. The high concentrations of fentanyl in the tissues may also indicate reduced metabolism. Unfortunately, we did not analyze the specimens for fentanyl metabolites as primary reference materials were unavailable from commercial supplies and request to the manufacturer of the drug were not answered. Clearance of unchanged fentanyl via the kidney is less than 8% of an I.V. dose. In this case, kidney concentrations were higher than

TABLE 1—*Toxicological findings.*

Tissue	Fentanyl Concentration
Blood	25 ng/mL
Brain	54 ng/g
Heart	94 ng/g
Kidney	69 ng/g
Liver	104 ng/g

previously reported cases involving I.V. deaths. This high concentration would not be expected under normal conditions for a transdermal delivery system and could be the result of increased unchanged fentanyl available for excretion via the kidneys.

Conclusion

This case demonstrates the need for caution in self-administration of transdermal fentanyl patches, in particular, the dangers inherent in the application of multiple patches which can result in the release of potentially toxic or lethal doses. This same caution would apply to nonprofessional care givers assisting in the application of fentanyl patches. It is important to keep in mind that the metabolism of fentanyl in the elderly is slowed and must be considered as a factor in the high concentrations achieved in this case. The potential for misuse of transdermal fentanyl patches (foul play, assisted suicide, and therapeutic mis-adventures) must be considered in any death associated with fentanyl toxicity.

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